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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/306,986	05/07/1999	THUAN QUOC TRINH	0942.4570001	4261

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STERNE KESSLER GOLDSTEIN & FOX PLLC
ATTORNEYS AT LAW
1100 NEW YORK AVENUE NW SUITE 600
WASHINGTON, DC 200053934

EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/306,986	TRINH ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-13,56 and 70-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-12,56 and 70-73* is/are rejected.

7)☒ Claim(s) *13,74 and 75* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants filing of an appeal brief on 5/1/2006 is acknowledged, however, upon further consideration, the finality of the previous office action has been removed and the following supplemental non-final office action deemed appropriate.

Claims 8-13, 56 and 70-75 remain at issue and are present for examination. Applicants' arguments filed on 5/1/2006, have been fully considered.

Claim Objections

Claims 13, 74 and 75 are objected to because of the following informalities: Claims 13, 74 and 75 are dependent on rejected claim 8. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 8-12, 56, 70-73 are rejected under 35 U.S.C. 102(b) as being anticipated by Major as evidenced by Deana and Belasco (Mol. Microbiology, Vol. 51, No. 4, pp 1205-1217, 2004).

Major teaches a rapid PCR method of screening for point mutations. The taught method involves ascertaining the presence of a desired mutation within the mutated fragment or within some vector into which the mutated fragment has been cloned.

Major teaches a method which comprises the synthesis of a nucleic acid molecule from a preparation comprising RNA and double-stranded DNA, said method comprising mixing the preparation with one or more DNA polymerases and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of a template nucleic acid molecule. The method taught by Major specifically involves the PCR amplification, using Taq DNA polymerase, of a DNA fragment from the expression plasmid, pBluescript 11 SK(+), either sampled directly from JM109 E. coli colonies or from a bacterial plasmid isolate. Major further teach that some primers, especially those with a 3'-terminal T.'T mismatch result in extra minor bands when bacterial colony lysates were used for the starting material. This thus decreases the sensitivity of the taught assay. Major does not teach the inclusion of ribonuclease in the taught method, however, the bacterial lysate mixture taught by Major et al. inherently comprises ribonuclease. The inclusion of ribonuclease in the mixture taught by Major is evidenced by Deana and Belasco (Mol. Microbiology, Vol 51 No. 4, pp 1205-1217, 2004) who teach that *E. coli* inherently comprise a number of Rnases that are capable of degrading single stranded RNA. It is noted that the reference Deana and Belasco is not available as prior art, however, this is unnecessary as this reference is only used to evidence that which is inherent in that method taught by Major.

Thus claims 8-12, 56, 70-73 are anticipated by Major.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-12, 56, 70, 71 and 73 under 35 U.S.C. 103(a) remain rejected as being unpatentable over Major (Biotechniques, Vol 12, No. 1, 1992, pages 40-43) and Maudru et al. (Journal of Virological Methods 66: 247-261, July 1997).

The rejection was stated in the previous office actions. In response to this rejection applicants have filed an appeal brief arguing applicants position.

Applicants continue to traverse the current rejection on the following basis. Applicants refer to the statements in the previous office action.

> While Major does not attribute background difficulties to contaminating RNA, one of skill in the art would realize that given the employment of the method of Major to bacterial lysates, there would be a substantial amount of background RNA in the preparation. This knowledge in combination with that taught by Maudru et al. stating that the background signal in a similar assay was found to be due to an intrinsic RNA-dependent DNA polymerase activity of the *Taq* DNA polymerase would lead one of skill in the art who was attempting to successfully use a PCR method to screen for small mutations to include a ribonuclease digestion step prior to PCR amplification as a means of making the assay more sensitive. In support of the above, applicants attention is drawn to Major, page 42, middle column, which states "the present results indicate that all three possible terminal T mismatches can be equally discriminated under standard PCR conditions, **especially** when using mini-prep DNA". Such a statement clearly supports that even Major recognized the taught method had different results or sensitivities depending on the template used (noting the reference to "especially"), although Major did not comment on the specific difference of the two different types of template preparations. One of skill in the

art would understand that the difference was likely the presence of contaminating material, such as RNA.

Applicants continue to argue the rejection on the basis that the position previously taken that one of skill in the art would have attributed the "Extra Minor Bands" mentioned in the Major reference to the presence of contaminating RNA in the reactions is incorrect. Applicants submit that Major did not attribute these extra minor bands to contaminating RNA, but rather to amplification products produced from oligonucleotides that have 3'-terminal nucleotide mismatches.

Applicants submit that the above reasoning is both logically and technically flawed based on the following:

Applicants continue to submit that a bacterial lysate contains many factors besides RNA (e.g., proteins, salts, lipids, signaling molecules, etc.) and that these other factors are absent from mini-prep DNA, and thus there is no reason why one of ordinary skill in the art would have specifically regarded RNA as the one factor responsible for the difference in 3'-terminal mismatch discrimination alluded to in Major. Applicants submit that the only such evidence is presented in applicant's own specification, which can not be used against applicants. This first point has again been considered in full, however found non-persuasive. As previously stated in the original rejection,

"Maudru et al. teach that the background signal of the PCR-based reverse transcriptase assay is due to an intrinsic **RNA-dependent** DNA polymerase activity of the Taq DNA polymerase enzyme and they teach that this background signal could be eliminated by the addition of a ribonuclease to the amplification reaction".

This previously presented evidence as taught by Maudru, is in part the basis of the conclusion of the components present in a bacterial lysate relative to a mini-prep, it is the RNA which is most likely the source of interference.

Applicants reference to Kwok et al. is acknowledged, however, not found persuasive, because it is irrelevant to the taught amplification of bacterial lysates. Similarly the presentation of the reference Charlieu is not considered relevant to the methods taught using bacterial lysates.

Secondly, applicants assert that a person of ordinary skill in the art would not have had any motivation to combine Maudru with Major as the references deal with entirely different non-analogous assay systems. Applicant's argument is acknowledged, however found nonpersuasive, because the basis to combine the references is as previously stated, based on the fact that both references teach methods of amplification of nucleic acids. Applicant's characterization of Maudru as being concerned with assaying the presence of reverse transcriptase in a sample is misleading. In support applicant's attention is directed to the title of Maudru which is "Elimination of background signals in a modified polymerase chain reaction-based reverse transcriptase assay".

Applicants complete argument is acknowledged, however continues to be found non-persuasive and the rejection of claims 8-12, 56, 70, 71 and 73 is maintained for the reason previously made of record and repeated above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
7/18/2006